

WE CLAIM:

1 1. An isolated heterodimeric receptor, which receptor comprises
2 an opioid receptor subunit and a second G-protein coupled receptor (GPCR) subunit,
3 wherein both receptor subunits are expressed endogenously in the same type of cell.

1 2. The heterodimeric receptor of claim 1, wherein the second
2 receptor is an opioid receptor that is distinct from the first opioid receptor.

1 3. The heterodimeric receptor of claim 1, wherein the second
2 receptor is a dopamine receptor.

1 4. The heterodimeric receptor of claim 1, wherein the second
2 receptor is an adrenergic receptor.

1 5. The heterodimeric receptor of claim 1, wherein the second
2 receptor is a chemokine receptor.

1 6. The heterodimeric receptor of claim 1, wherein the opioid
2 receptor is a delta opioid receptor and the second receptor is selected from the group
3 consisting of kappa opioid receptor, mu opioid receptor, D2 dopamine receptor, and
4 β_2 -adrenergic receptor.

1 7. The heterodimeric receptor of claim 1, wherein the opioid
2 receptor is a kappa opioid receptor and the second receptor is selected from the group
3 consisting of delta opioid receptor, D2 dopamine receptor, α_2 -adrenergic receptor, β_2 -
4 adrenergic receptor, CCR5, and CXCR4.

1 8. The heterodimeric receptor of claim 1, wherein the opioid
2 receptor is a mu opioid receptor and the second receptor is selected from the group
3 consisting of delta opioid receptor and α_2 -adrenergic receptor.

1 9. The heterodimeric receptor of claim 1, wherein the opioid
2 receptor is a fusion protein comprising a sequence of a functional opioid receptor
3 protein and a tag sequence.

1 10. The heterodimeric receptor of claim 1, wherein the second
2 receptor is a fusion protein comprising a sequence of a functional second receptor
3 protein and a tag sequence.

1 11. A recombinant host cell that expresses a functional
2 heterodimeric receptor, which receptor comprises an opioid receptor subunit
3 expressed from an expression vector introduced into the host cell, and a second G-
4 protein coupled receptor (GPCR) subunit expressed from an expression vector
5 introduced into the host cell, wherein both receptor subunits are expressed
6 endogenously in the same type of cell.

1 12. The host cell of claim 11, wherein the second receptor is a
2 different opioid receptor or a covalently associated opioid receptor.

1 13. The host cell of claim 11, wherein the second receptor is a
2 dopamine receptor.

1 14. The host cell of claim 11, wherein the second receptor is an
2 adrenergic receptor.

1 15. The host cell of claim 11, wherein the second receptor is a
2 chemokine receptor.

-68-

1 16. The host cell of claim 11, wherein the opioid receptor is a delta
2 opioid receptor and the second receptor is selected from the group consisting of kappa
3 opioid receptor, mu opioid receptor, D2 dopamine receptor, and β_2 -adrenergic
4 receptor.

1 17. The host cell of claim 11, wherein the opioid receptor is a
2 kappa opioid receptor and the second receptor is selected from the group consisting of
3 delta opioid receptor, D2 dopamine receptor, α_2 -adrenergic receptor, β_2 -adrenergic
4 receptor, CCR5, and CXCR4.

1 18. The host cell of claim 11, wherein the opioid receptor is a mu
2 opioid receptor and the second receptor is selected from the group consisting of delta
3 opioid receptor and α_2 -adrenergic receptor.

1 19. A method of screening for a compound that modulates a
2 property of a heterodimeric receptor, which receptor comprises an opioid receptor
3 subunit and a second G-protein coupled receptor (GPCR) subunit, wherein both
4 receptor subunits are expressed endogenously in the same type of cell, which method
5 comprises observing a change in a property of the heterodimeric receptor contacted
6 with a candidate compound.

1 20. The method according to claim 19, wherein the heterodimeric
2 receptor property is trafficking of the heterodimeric receptor.

1 21. The method according to claim 19, wherein the heterodimeric
2 receptor property is binding affinity for a ligand.

1 22. The method according to claim 19, wherein the heterodimeric
2 receptor property is activation of a signal transduction pathway.

-69-

1 23. The method according to claim 22, wherein the signal
2 transduction pathway is selected from the group consisting of cAMP production and
3 MAPK phosphorylation.

1 24. A bispecific, bivalent compound comprising an opioid receptor
2 ligand bound to a second G-protein coupled receptor ligand, wherein the second
3 receptor is expressed endogenously in a type of cell that endogenously expresses the
4 opioid receptor.

1 25. The compound of claim 24, wherein both ligands are agonists.

1 26. The compound of claim 24, wherein both ligands are
2 antagonists.

1 27. The compound of claim 24, wherein both ligands are kappa
2 receptor ligands.

1 28. The compound of claim 24, wherein the opioid receptor ligand
2 is a kappa receptor agonist and the second receptor ligand is a delta receptor agonist.

1 29. A pharmaceutical composition comprising synergistically
2 effective amounts of a ligand of a delta opioid receptor and a ligand of a second
3 receptor selected from the group consisting of kappa opioid receptor, mu opioid
4 receptor, D2 dopamine receptor, and β_2 -adrenergic receptor.

1 30. A pharmaceutical composition comprising synergistically
2 effective amounts of a ligand of a kappa opioid receptor and a ligand of a second
3 receptor selected from the group consisting of delta opioid receptor, D2 dopamine
4 receptor, α_2 -adrenergic receptor, β_2 -adrenergic receptor, CCR5, and CXCR4.

-70-

1 31. A pharmaceutical composition comprising synergistically
2 effective amounts of a ligand of a mu opioid receptor and a ligand of a second
3 receptor selected from the group consisting of delta opioid receptor and α_2 -adrenergic
4 receptor.

1 *but α_2* 32. A method of treating a disease or disorder selected from the
2 group consisting of chronic pain, drug abuse, schizophrenia, depression, central
3 reward pathway, HIV infection, cardiovascular disease, and hypertension, which
4 method comprises administering a therapeutically effective dose of a compound of
5 claim 24 or a pharmaceutical composition of claim 29, 30, or 31.

Add A3